

REVIEW

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Photobiomodulation in experimental models of Alzheimer's disease: state-of-the-art and translational perspectives

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Abstract

Alzheimer's disease (AD) poses a significant public health problem, affecting millions of people across the world. Despite decades of research into therapeutic strategies for AD, effective prevention or treatment for this devastating disorder remains elusive. In this review, we discuss the potential of photobiomodulation (PBM) for preventing and alleviating AD-associated pathologies, with a focus on the biological mechanisms underlying this therapy. Future research directions and guidance for clinical practice for this non-invasive and non-pharmacological therapy are also highlighted. The available evidence indicates that different treatment paradigms, including transcranial and systemic PBM, along with the recently proposed remote PBM, all could be promising for AD. PBM exerts diverse biological effects, such as enhancing mitochondrial function, mitigating the neuroinflammation caused by activated glial cells, increasing cerebral perfusion, improving glymphatic drainage, regulating the gut microbiome, boosting myokine production, and modulating the immune system. We suggest that PBM may serve as a powerful therapeutic intervention for AD.

Keywords Alzheimer's disease (AD), Photobiomodulation (PBM), Neurodegeneration, Therapy, Experimental models

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting millions of people across the world [1]. With the continued aging of the population, the prevalence of AD is expected to further rise in the coming decades [2]. AD is characterized by the extracellular accumulation of amyloid-beta (A β) plaques and the

presence of intracellular neurofibrillary tangles (NFTs). However the etiology of AD involves a complicated pathophysiology [3], and there is no agreement on the most important causes of AD. Individuals with AD typically experience progressive cognitive impairment, and face challenges in problem-solving, language, and other cognitive functions [3, 4]. Despite an enormous scientific effort focusing on this disease, there are currently limited disease-modifying therapies. To date, several anti-amyloid monoclonal antibodies have been approved for treating early AD patients. Nevertheless, the high cost and potential adverse effects of these medications have driven scientists to explore alternative therapeutic hypotheses and strategies [5–8]. In this context, treatment strategies for this disease have been proposed to shift from single to multiple targets, and a vast array of new therapeutic approaches for AD is under investigation [9, 10].

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Photobiomodulation (PBM), also known as low-level laser (light) therapy, is a promising modality to treat a wide variety of pathological conditions, such as wound healing, pain, inflammation, and tissue injury [11, 12]. PBM is a non-pharmacological and non-invasive intervention, involving exposing cells or tissue to low levels of red and/or near-infrared (NIR) light (wavelengths between 600–1100 nm) [13]. This low-level irradiation triggers various biological processes, including the modulation of mitochondrial dynamics, inhibition of inflammatory and apoptotic signaling, as well as the secretion of neurotrophic factors [14, 15]. Recently, the application of PBM therapy for neurological conditions, particularly AD and other age-related neurodegenerative diseases, has sparked increasing interest [12, 16]. The therapeutic potential of PBM for AD or dementia has been widely reported in experimental animal models and in some preliminary clinical trials [17–20].

In this review, we summarize the current understanding of the biological mechanisms underlying the therapeutic benefits of PBM for AD, with a focus on knowledge gained from studies in preclinical animal models. We then discuss the limitations of existing studies, as well as the challenges inherent in clinical translation. We hope this state-of-the-art review will provide a guide for future research in this area.

Treatment paradigms of PBM for AD

The dose of PBM for therapeutic purposes can be determined by dividing the total irradiation time (in seconds) by the power output (in mW/cm²), then dividing the result by 1000. This value is expressed as J/cm² and is known as the fluence or energy density. Several different paradigms for treating brain diseases with PBM have been reported. These include transcranial, intranasal, intravascular, and systemic PBM, as well as the recently proposed remote PBM [12, 21]. Given the limited research on intranasal and intravascular PBM approaches, this review will primarily focus on the biological mechanisms of transcranial, systemic, and remote PBM.

Transcranial PBM is the most studied PBM paradigm for the treatment of AD. This involves the non-invasive delivery of visible and/or NIR light, typically using light-emitting diodes (LED) applied to the head and brain regions for appropriate lengths of time (typically 10–30 min) [13, 22]. The primary effects of transcranial PBM with various light parameters in cell, animal, and human studies have been systematically reviewed elsewhere [23, 24]. These reviews highlight the potential of this therapy against neurodegeneration. In contrast, systemic PBM tested in preclinical studies has involved placing animals under an irradiation apparatus

and exposing their entire bodies to an LED array located overhead [25, 26]. Various whole-body light pods have also been developed to offer a more accessible PBM treatment option for human patients [27, 28].

Remote PBM is a novel concept involving the application of PBM to peripheral tissues/organs such as the abdomen or the legs, which has been suggested to indirectly affect the brain via as yet unknown mediators [21, 29]. This approach stems from the observation that PBM can elicit systemic effects that contribute to the protection of distant tissues [30]. In an analogy to the technique of remote ischemic conditioning, scientists have coined the term “remote PBM” to describe this phenomenon [30]. Despite the limited understanding of its mechanisms to date, experimental animal studies have reported some neuroprotective effects of remote PBM against AD. Therefore remote PBM is considered to be promising for future clinical applications [31–33].

Regardless of the specific treatment paradigm employed, the well-accepted mechanism underlying the effects of PBM is that the light can be absorbed by cytochrome c oxidase (CCO), the terminal enzyme of the mitochondrial electron transport chain (ETC) [34, 35]. This enzyme catalyzes the transfer of electrons from cytochrome c to molecular oxygen in the terminal step of the ETC. This electron transfer process is coupled with the pumping of protons across the inner mitochondrial membrane, establishing an electrochemical gradient that drives the synthesis of adenosine triphosphate (ATP) by ATP synthase [36]. CCO contains two heme centers and two copper centers, which serve as molecular chromophores to absorb photons of red-to-near-infrared wavelengths [22, 37]. The absorption of photons delivered by PBM increases the activity of CCO and the synthesis of ATP, boosting mitochondrial function and triggering the initiation of various cellular processes [22, 38]. PBM may also lead to the dissociation of inhibitory nitric oxide (NO) from the CCO molecule, which could further facilitate electron transfer [39]. However, recent evidence suggests that CCO may not be the only target of PBM. In cells lacking CCO, PBM can still exert biological effects [40]. Additionally, various new biological effects of PBM have been reported recently, which will be discussed in detail in the following chapters. A diagram illustrating PBM treatment paradigms and the general mechanisms of action is provided in Fig. 1.

Biological mechanisms underlying the benefits of transcranial PBM for AD

PBM-activated cellular signaling

Historically, the accumulation of A β plaques and NFTs formed by pathologically assembled tau proteins has been considered central to the progression of AD. A β plaques and NFTs are thought to be the primary contributors, initiating diverse signaling cascades that ultimately

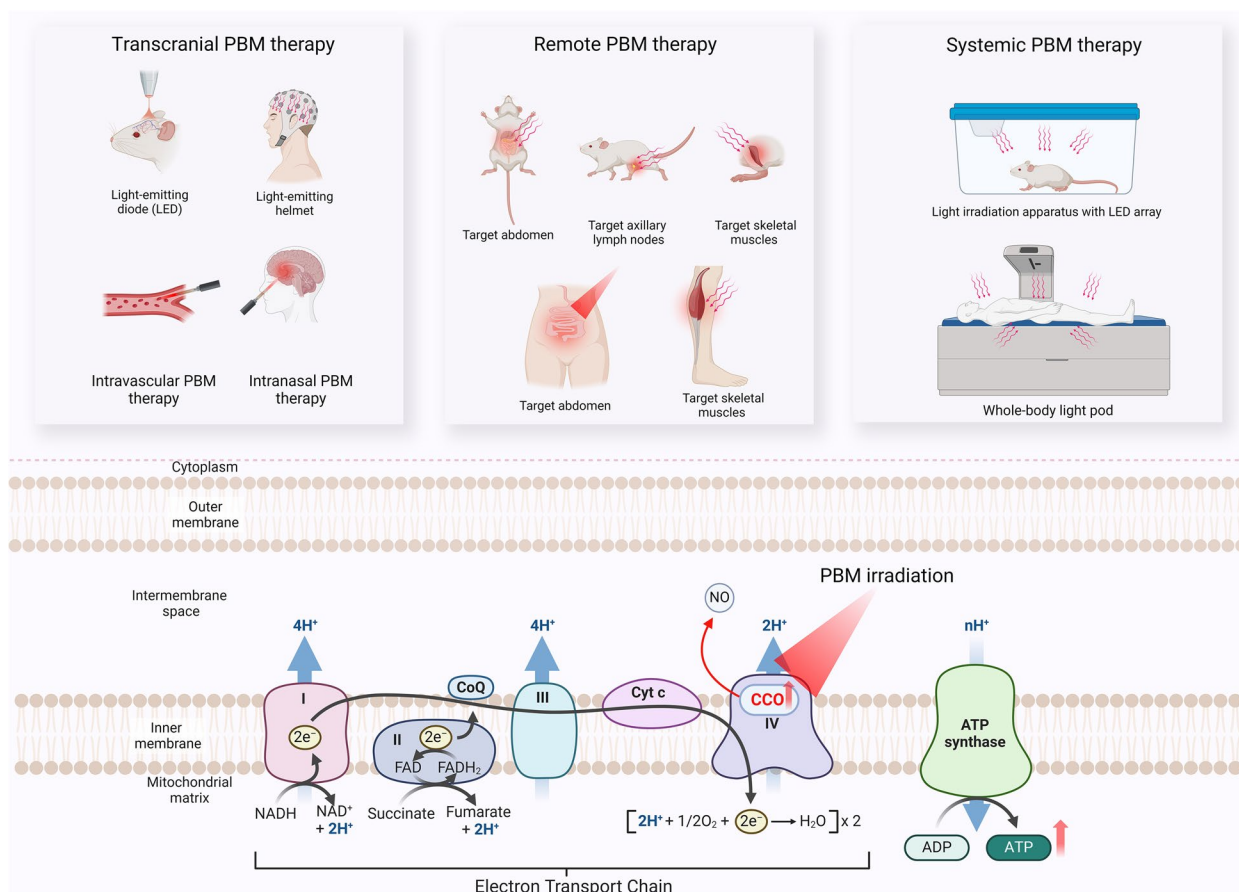


Fig. 1 Overview of different PBM treatment paradigms for AD and an illustration showing the mechanisms traditionally considered to underlie the action of PBM. Abbreviations: LED, light-emitting diode; PBM, photobiomodulation; CCO, cytochrome c oxidase; ATP, adenosine triphosphate; NO, nitric oxide

result in synaptic dysfunction and neural degeneration [41, 42]. Intriguingly, mounting evidence suggests that transcranial PBM could attenuate these AD pathological hallmarks and signaling cascades. A 4-week treatment with transcranial PBM (670 nm, continuous wave, 4 J/cm² applied to the head daily) has been reported to reduce hyperphosphorylated tau and neurofibrillary tangles in K3 mice, a transgenic mouse model with tau pathology [43]. Using the same parameters, a reduced Aβ burden was also observed in APP/PS1 mice, a transgenic mouse model engineered to develop Aβ pathology [43].

Research during the past decade has significantly advanced our understanding of the cellular signaling pathways activated by transcranial PBM (Fig. 2). In cultured neuron-like cells, PBM treatment (632.8 nm, continuous wave, 0.156 J/cm²-0.624 J/cm², single treatment) triggered PKC signaling-dependent upregulation of the anti-apoptotic protein Bcl-2 and inhibited the pro-apoptotic protein Bax, thereby preventing Aβ²⁵⁻³⁵-induced cellular apoptosis [44].

Other in vitro studies have shown that PBM can target the Akt/GSK3b/β-catenin pathway to counteract Aβ-induced cell apoptosis [45]. PBM treatment (632.8 nm, continuous wave, 2 J/cm², single treatment) activated Akt while also inactivating the GSK3b/β-catenin pathway. This, in turn, led to the enhanced nuclear translocation of β-catenin and increased its TCF/LEF-dependent transcriptional activity, thus promoting cell survival [45].

Transcranial PBM could also alter the signaling pathways implicated in Aβ processing. Aβ peptide is derived from the cleavage of amyloid precursor protein (APP). The processing of APP involves two distinct pathways; the non-amyloidogenic pathway and the amyloidogenic pathway [46, 47]. In the amyloidogenic pathway, APP is cleaved by β-secretase, also known as β-site APP cleaving enzyme 1 (BACE1). This cleavage generates soluble APPβ (sAPPβ). The remaining C-terminal fragment subsequently undergoes proteolytic processing by γ-secretase, resulting in the production of Aβ peptides

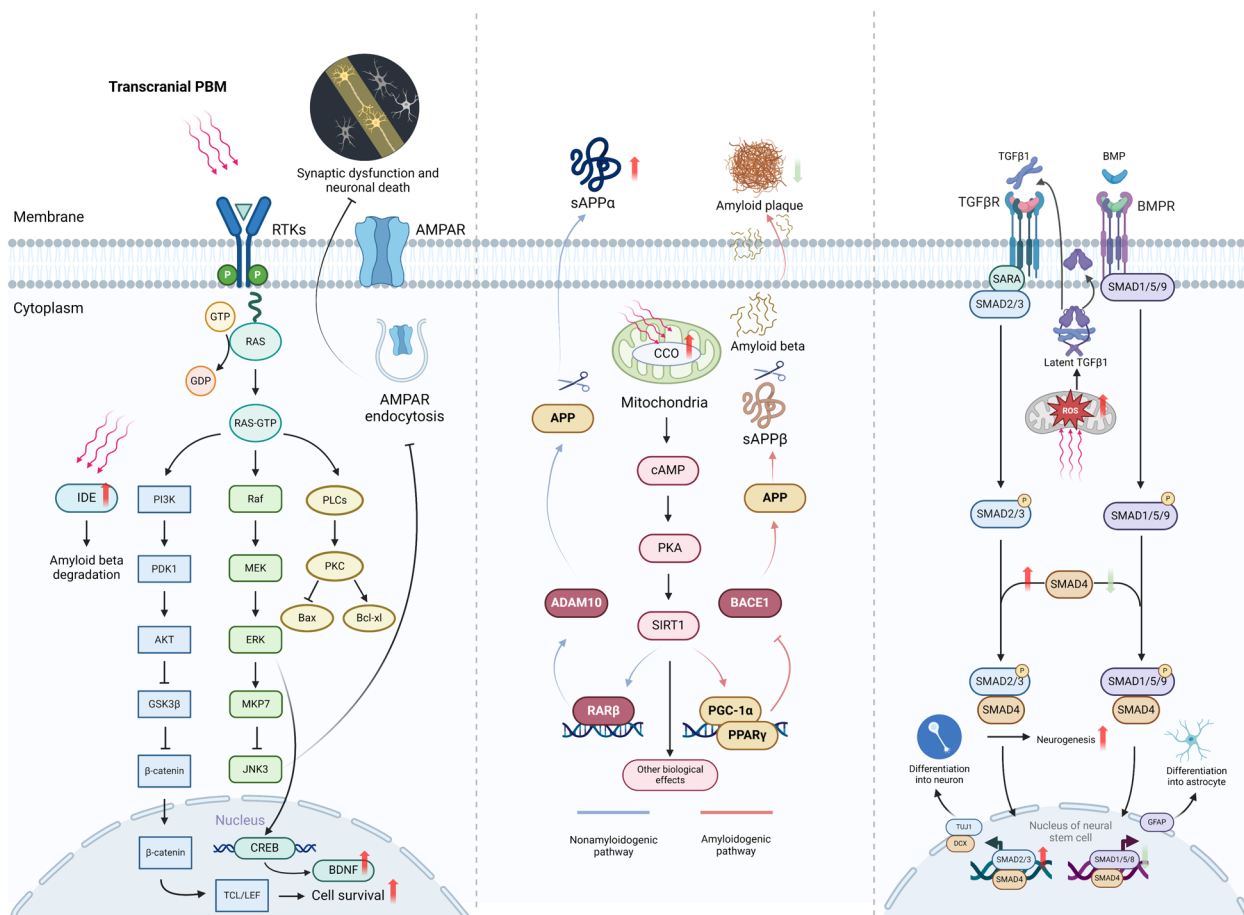


Fig. 2 Summary of signaling pathways activated by transcranial PBM and subsequent biological effects. Abbreviations: PBM, photobiomodulation; RTKs, receptor tyrosine kinases; AMPAR, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; IDE, insulin-degrading enzyme; CREB, cAMP response element-binding protein; BDNF, brain-derived neurotrophic factor; CCO, cytochrome c oxidase; APP, amyloid precursor protein; PGC1- α , peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPAR γ , peroxisome proliferator-activated receptor gamma; ADAM10, a disintegrin and metalloproteinase domain-containing protein 10; TGF β -1, transforming growth factor beta 1, TGF β R, transforming growth factor beta receptor; BMP, bone morphogenetic protein; BMPR, Bone morphogenetic protein receptor; ROS, reactive oxygen species

[48]. Conversely, in the non-amyloidogenic pathway, APP is cleaved by α -secretase, e.g. a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) [49]. This cleavage yields soluble APP alpha (sAPP α) and a C-terminal fragment, precluding the formation of A β peptides [49]. Therefore, approaches that lead to the switching of APP processing into the non-amyloidogenic pathway have been proposed to be a disease-modifying strategy for AD [48, 50]. Of note, in a transgenic AD mouse model, a-30 day transcranial PBM treatment (632.8 nm, continuous wave, 2 J/cm² at the hippocampus level daily) shifted APP processing toward the non-amyloidogenic pathway [51]. APP/PS1 mice treated with transcranial PBM showed a reduced A β burden, while the levels of full-length APP and the main proteolytic enzymes (insulin-degrading enzyme, IDE and neprilysin, NEP) responsible for A β degradation remained

unchanged [51]. Consistent with these findings, transcranial PBM also increased the level of sAPP α and decreased the level of sAPP β , accompanied by the upregulation of ADAM10 and downregulation of BACE1 protein levels. In vitro experiments further suggested that this shift in the APP processing pathway was mediated by increased CCO activity and subsequent activation of the PKA/SIRT1 signaling pathway [51]. Interestingly, long-term transcranial PBM appears to elicit more profound biological effects than short-term treatment. Indeed, a decrease in sirtuin1, encoded by the SIRT1 gene, has been linked to the progression of AD [52–54]. A postmortem study has revealed that reduced brain sirtuin1 aligns with the accumulation of tau in AD patients [55]. As a key metabolic regulator, SIRT1 exhibits neuroprotective properties, such as inhibiting tau hyperphosphorylation, alleviating oxidative stress and neuroinflammation, and

modulating synaptic plasticity [56]. These aspects have been extensively discussed in previous reviews [53, 56]. Notably, a recent study demonstrated that PBM therapy restored SIRT1 expression in chronically stressed mice [57]. This suggests that PBM might activate SIRT1/sirtuin1 and associated signals, therefore exerting diverse biological effects. Additionally, despite the exact mechanism remaining unknown, a 14-week transcranial PBM treatment (610 nm, continuous wave, 2 J/cm² daily), initiated at 2 months of age, significantly elevated the levels of IDE, with reduced A β accumulation and less neuronal loss [58].

Transcranial PBM could also protect against AD-associated synaptic dysfunction by attenuating AMPA receptor endocytosis [59]. Synaptic dysfunction is another major pathological process that might be responsible for memory impairment in the progression of AD [60, 61]. AMPA receptors, typically located on the postsynaptic membrane of neurons, mediate fast excitatory synaptic transmission [62]. When activated by neurotransmitters, AMPA receptors are internalized into the postsynaptic neuron, a process known as AMPA receptor endocytosis [62, 63]. The dynamic interplay between AMPA receptor endocytosis and exocytosis, leading to the insertion of receptors into the membrane, allows synapses to adapt to changes in neuronal activity. This process facilitates synaptic plasticity, the basic foundation of learning and memory [64, 65]. Aberrant AMPA receptor endocytosis has been implicated in AD-associated memory impairment [66, 67]. Moreover, the inhibition of AMPAR endocytosis could prolong memory retention in normal animals and ameliorate memory impairment in an experimental animal model of AD [68]. Reduction of A β ¹⁻⁴² results in JNK signaling-dependent endocytosis of surface AMPA receptors and ameliorates subsequent dendrite injury [59]. In contrast, transcranial PBM treatment (632.8 nm, continuous wave, 2 J/cm² at the hippocampus level daily for 30 days) in APP/PS1 mice activated the ERK/MKP7 signaling pathway, which further inhibited JNK3 to attenuate AMPA receptor endocytosis and rescued synaptic pathology [59].

As a non-pharmacological intervention, transcranial PBM recently has been proven to modulate neurogenesis, and trigger the formation of new neurons from neural stem and progenitor cells [69, 70]. The dentate gyrus of the hippocampus serves as a central hub for adult neurogenesis in mammals [71]. While there is a growing body of evidence suggesting that hippocampal neurogenesis likely continues throughout life, it has been shown to diminish with aging and is compromised in AD [71, 72]. Targeted stimulation of neurogenesis has been shown to restore AD-linked impairment of synaptic formation and memory in an experimental animal

model [73]. Notably, the fate of neural stem cells is regulated by various signaling pathways, including TGF β and BMP signaling, which govern their differentiation into either neurons or astrocytes [74, 75]. In one recent study using both in vivo and in vitro models, it was observed that PBM (in vivo, 635 nm, continuous wave, 6 J/cm² at cortex level daily, for 1 month; in vitro, 2 J/cm², single treatment) boosted the interaction of the transcription factors Smad2/3 with Smad4 and triggered the differentiation of neural stem cells into immature neurons, which resulted in enhanced neurogenesis [70]. Moreover, photoactivation of Smad2/3 competitively reduced the interaction of Smad1/5/9 with Smad4, leading to decreased differentiation into astrocytes [70]. This shift in the direction of neural stem cell differentiation is mediated by the production of reactive oxygen species (ROS) in response to PBM. This, in turn, activated the TGF β /Smad signaling pathway, initiating downstream effector molecules and cellular processes [70]. PBM (632.8 nm, continuous wave, 0.5, 1, 2, and 4 J/cm², single treatment) could also activate the transcription factor CRE-binding protein (CREB) in an ERK-dependent manner [76]. This activation of CREB further triggered the expression of brain-derived neurotrophic factor (BDNF), a neurotrophin implicated in neuronal survival, differentiation, and plasticity [76, 77]. The inhibition of ERK abrogated PBM-activated CREB/BDNF, thereby eliminating the beneficial effects of PBM in mitigating A β -induced neuron loss and dendritic atrophy [76].

Transcranial PBM may also affect intraneuronal signaling. In cultured primary neurons, PBM treatment mitigated neuronal damage induced by oxygen and glucose deprivation, leading to the restoration of neuronal viability [78]. Nevertheless, the potential effects of transcranial PBM on intraneuronal signaling in the context of AD remain to be demonstrated by future research.

Taken together, transcranial PBM appears capable of activating a variety of intracellular signaling molecules and signaling pathways. In light of the multifactorial nature of AD, the ability of transcranial PBM to initiate multiple intracellular signals with different beneficial effects encourages optimism concerning its therapeutic potential in AD.

PBM and mitochondrial function

One important biological effect of PBM is its ability to regulate mitochondrial function [38, 39]. PBM can increase mitochondrial membrane potential, partially through regulating mitochondrial redox signaling, thus leading to increased ATP production [39]. Intriguingly, under normal physiological conditions, PBM appears to increase intracellular ROS and trigger downstream signaling pathways. Conversely, under pathological

conditions with already existing oxidative stress, PBM tends to inhibit ROS production by restoring the mitochondrial potential to its healthy state [39]. Utilizing 31P magnetic resonance spectroscopy, it was found that 670 nm transcranial PBM (20 min) increased the ATP synthase flux rate in the brains of older adults [79]. This observation was initial clinical evidence supporting the efficacy of PBM in enhancing mitochondrial function in the human brain.

Emerging research suggests that mitochondrial dysfunction, which may either derive from Aβ deposition or occur independently of Aβ pathology, potentially presents a brain “energy crisis” and contributes to the onset of AD [80, 81]. Two recent studies have presented evidence that transcranial PBM could rescue mitochondrial dysfunction observed in the progression of AD [17, 82]. A 5-day transcranial PBM (808 nm, continuous wave, 3 J/cm² at the cortex level and ~1 J/cm² at the hippocampus level daily) rescued Aβ¹⁻⁴² infusion-triggered mitochondrial dysfunction [82]. This intervention conferred multiple benefits, including the preservation of mitochondrial dynamics, inhibition of mitochondrial fragmentation, restoration of mitochondrial membrane potential, facilitation of mitochondrial homeostasis, and increased cytochrome c oxidase activity and ATP synthesis [82]. In another study, a transgenic rat model of AD was used to investigate the efficacy of long-term transcranial

PBM preconditioning for AD [17]. At 18 months of age, TgF344-AD rats exhibited increased mitochondrial fragmentation, accompanied by oxidative damage and abnormal mitochondrial dynamics, characterized by an increase in mitochondrial fission proteins and a reduction in mitochondrial fusion proteins [17]. Strikingly, daily transcranial PBM treatment (from 2 to 18 months old, 3 times/week, 808 nm, continuous wave, 3 J/cm² at the cortex level) reversed these pathological alterations and restored mitochondrial homeostasis [17]. Further experiments revealed that the beneficial effects conferred by PBM were mediated by neuronal hemoglobin α, a component of nerve cells essential for intraneuronal oxygen homeostasis [17, 83]. A diagram illustrating these findings is presented in Fig. 3.

PBM, glial cells, and neuroinflammation

Studies in recent years have firmly established neuroinflammation to be a central player in AD pathogenesis [84, 85]. Astrocytes and microglia, two major neural cell types, are recognized as key contributors to the initiation of the inflammatory response in the brain [86, 87]. In response to injury, disease, or infection in the CNS, activated microglia and astrocytes release both inflammatory mediators and neuroprotective factors [88, 89]. These factors may play distinct roles in shaping the local microenvironment [90, 91]. Despite the limited understanding

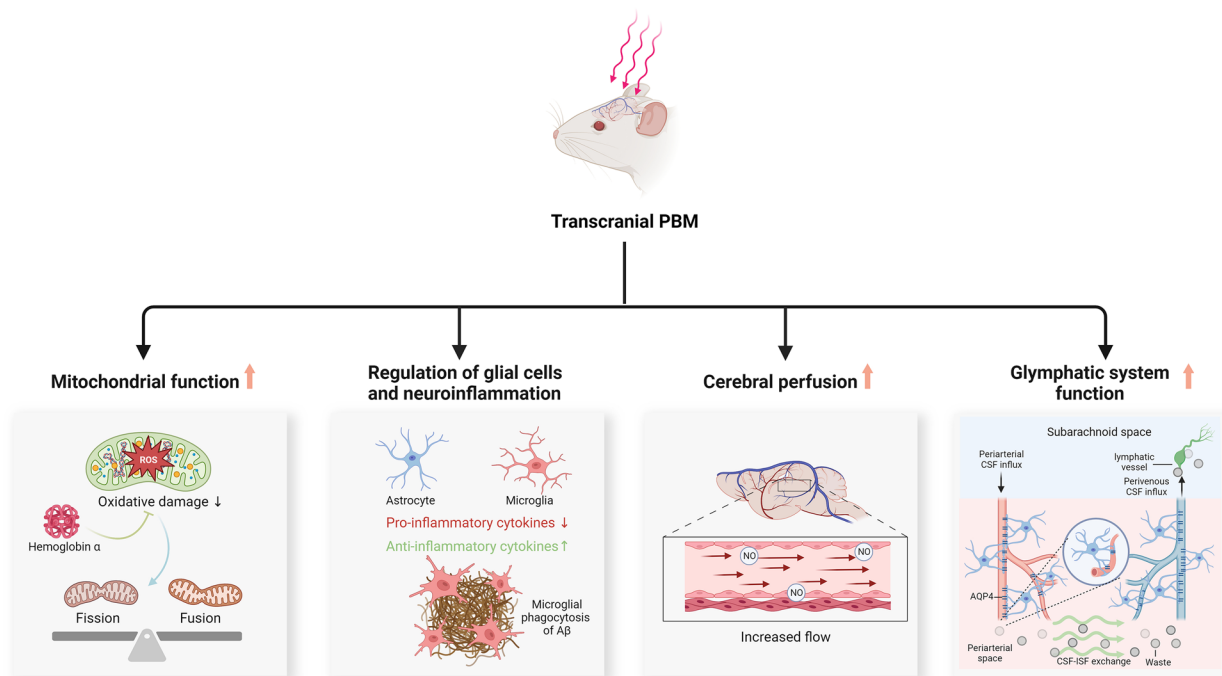


Fig. 3 Additional proposed mechanisms of action for transcranial PBM. Abbreviations: PBM, photobiomodulation; ROS, reactive oxygen species; Aβ, amyloid beta; NO, nitrogen oxide; CSF, cerebrospinal fluid; AQP4, aquaporin 4; ISF, interstitial fluid

of these cellular processes and the complexity of the physiology of glial cells, their “double-edged sword” role in AD has been recognized [92, 93].

Preliminary findings suggest that transcranial PBM may modulate the polarization of glial cells to limit pro-inflammatory signals [17, 82, 94]. Microglial cells exposed to A β exhibit increased levels of pro-inflammatory cytokines, which could be suppressed by PBM treatment (808 nm, continuous wave, 9 J/cm², single treatment) [94]. Furthermore, there is evidence that transcranial PBM triggers the polarization of microglia and astrocytes into neuroprotective/anti-inflammatory phenotypes [17]. The TgF344-AD rat model shows elevated pro-inflammatory M1 microglia and A1 pro-inflammatory astrocytes in the brain. Similar results were observed in microglial and astrocytal cultures treated with A β [17]. Remarkably, both in vivo transcranial and in vitro treatment with PBM (808 nm, continuous wave, 3 J/cm² at the cortex level, three times per week, last for 16 months) shifted pro-inflammatory glial cells into anti-inflammatory/neuroprotective phenotypes. This transformation was accompanied by decreased levels of pro-inflammatory cytokines and elevated levels of anti-inflammatory cytokines [17]. As the resident immune cells of the CNS, microglia are implicated in the clearance of A β through phagocytosis, a physiological process negatively correlated with inflammatory mediators [95, 96]. Application of 808 nm PBM in this context, appears to activate microglia-mediated phagocytosis of A β . This was shown by the increased recruitment of microglia to the surrounding amyloid plaques following PBM treatment [17, 94]. Another study revealed the role of microglia-derived exosomes in the anti-inflammatory effects conferred by PBM [97]. In cultured BV-2 microglial cells, PBM (1070 nm, 10 Hz, 2 and 4 J cm²) remarkably inhibited A β -triggered inflammation, an effect that was abolished by the blockade of exosome biogenesis/release [97]. Moreover, the administration of exosomes derived from microglia exposed to 1070-nm light attenuated neuroinflammation and improved spatial learning and memory ability in 5xFAD AD mice [97]. This suggests that the contents of microglia-derived exosomes are crucial for the anti-inflammatory effects of PBM. These findings offer new mechanistic insights into the regulatory effects of PBM on inflammation and glial cells.

PBM and cerebral perfusion

Normal cerebral perfusion is crucial for maintaining proper neuronal function. Disruptions in perfusion can negatively impact both brain structure and function, potentially contributing to cognitive decline in the elderly population [98, 99]. Moreover, global and regional cerebral hypoperfusion has been widely observed in AD

throughout its course [100–102]. A recent cross-sectional study also suggested an elevated risk of mild cognitive impairment and dementia associated with cerebral hypoperfusion [103].

Although direct research on the impact of transcranial PBM on AD-associated cerebral hypoperfusion is presently lacking, the available evidence suggests that PBM may play a role in sustaining regional cerebral blood flow [19]. In a pilot study, fourteen patients with mild cognitive impairment underwent transcranial PBM (applied to the vertebral and internal carotid arteries), and regional perfusion was measured at baseline and after PBM treatment [19]. While no statistically significant differences were observed post-treatment, notable trends emerged in certain brain regions, including the medial prefrontal cortex, lateral prefrontal cortex, anterior cingulate cortex, and occipital lateral cortex [19]. Furthermore, these patients reported enhanced overall cognitive function after PBM treatment [19]. PBM irradiation over the right prefrontal cortex also enhanced regional cerebrovascular oxygenation in healthy adults [104]. One animal study offered mechanistic insights into the regulation of cerebral perfusion in response to transcranial PBM [105]. Transcranial PBM (808 nm, 1.6 W/cm² for 15–45 min) increased local CBF by 30% compared to control animals, accompanied by an elevation in cerebral NO, a crucial factor in cerebral blood flow regulation [105, 106]. Importantly, the effect of PBM could be abolished by administering L-NAME, an inhibitor of NO synthase [105].

It should be noted that the impaired bioavailability of NO has been proposed to be a mechanism underlying cognitive decline and AD-associated cerebral hypoperfusion [107]. A study using cultured human endothelial cells and human neuroblastoma cells provided further insight into the mechanisms behind PBM-induced NO production [108]. Three different PBM parameters (808 nm, 1064 nm, and 1270 nm, continuous wave, 10 mW/cm²) triggered the release of NO from human endothelial cells, accompanied by an elevated expression of phosphorylated endothelial nitric oxide synthase (eNOS) [108]. In contrast, cultured neuronal cells expressing neuronal nitric oxide synthase (nNOS) showed no appreciable NO generation following PBM irradiation, suggesting that increased eNOS and its phosphorylation may play a pivotal role in PBM-triggered NO production. A recent study further uncovered that phosphorylation of eNOS is crucial for enhanced CBF following transcranial PBM treatment [109]. A 5-min exposure to a 1064-nm laser at an irradiance of 50 mW/cm² significantly elevated CBF levels compared to baseline, accompanied by an increase in eNOS phosphorylation. Conversely, mice incapable of phosphorylating eNOS exhibited no change in CBF after the same PBM treatment procedure [109].

Although remaining controversial, it has been proposed that the dissociation of inhibitory NO from CCO by the action of PBM may also contribute to increased NO levels [39]. Consequently, the enhanced NO levels resulting from PBM may increase cerebral blood flow, therefore counteracting AD-associated cerebral hypoperfusion. The proposed mechanism for this effect is outlined in Fig. 3.

PBM and the glymphatic system

The glymphatic system, also known as the meningeal lymphatic system, is a recently discovered macroscopic waste clearance system in the brain [110]. The glymphatic system comprises perivascular spaces, astroglial cells, interstitial spaces in neural tissue, and perivenous spaces. It plays a crucial role in the clearance of soluble proteins (e.g., A β) and other metabolites from the CNS [110, 111]. In the glymphatic system, cerebrospinal fluid (CSF) penetrates the brain through the periarterial spaces. Subsequently, CSF traverses into the interstitium via the interaction of perivascular astrocytic and aquaporin-4 (AQP4), facilitating the drainage of interstitial fluid (ISF) and its solutes through perivenous pathways [112, 113]. Furthermore, AQP4, a key member of the aquaporin water channel protein family, is prominently expressed on the end feet of astrocytes near the vascular perivascular spaces. This polarized distribution of AQP4 is thought to facilitate the rapid exchange of CSF with ISF and support effective glymphatic drainage [114, 115].

An impaired function of the glymphatic system is a common feature of various neurodegenerative disorders, including AD, Parkinson's disease, and multiple sclerosis [116–118]. Compromised AQP4 polarization and the limited exchange of CSF and ISF have been observed in an experimental animal model of AD [115, 116]. Inhibition or deletion of AQP4 potentiated the deposition of phosphorylated tau in the brain, along with the exacerbation of neurodegeneration [115, 116]. Similarly, suppressing glymphatic drainage by ligating deep cervical lymph nodes aggravated A β plaque formation and memory impairment in 5xFAD mice [119]. A recent neuroimaging study demonstrated a negative correlation between whole-brain glymphatic activity and the deposition of amyloid and tau, along with positive correlations with cognitive scores [120].

Notably, several lines of evidence suggest that transcranial PBM may serve as a non-invasive method to enhance glymphatic drainage and clearing functions [121–123]. When treated with 1267 nm transcranial PBM (continuous wave, 4 J/cm² for pups and 9 J/cm² for adult mice at the cortex level, for 7 days), there was a significant improvement in the removal of infused macromolecules from the lateral ventricle into deep cervical

lymph nodes [121]. This effect was achieved through the dilation of basal meningeal lymphatic vessels triggered by PBM [121]. Similarly, employing these PBM parameters also enhanced the clearance of macromolecules through the glymphatic pathway in mice infused with A β and promoted the aggregation of A β around meningeal lymphatic vessels [122, 123]. Notably, PBM typically involves modulating cellular responses through non-thermal mechanisms. The wavelength range, starting from 1100 nm and above is thought to be absorbed by water, potentially causing heating effects and damage to brain tissues [124]. However, measurements at the the surface of cortex indicated that transcranial PBM at 1267 nm, did not induce any alterations in brain temperature and no morphological changes were observed [121]. This suggests the potential application of transcranial PBM at longer wavelengths.

A more recent study has provided direct evidence of transcranial PBM's effect on AD-associated glymphatic pathology [125]. In 6-month-old 5xFAD AD mice, a 4-week transcranial PBM intervention (continuous wave, 6–30 J/cm²) significantly alleviated learning and memory deficits while enhancing glymphatic drainage [125]. Notably, further investigation revealed that the enhanced lymphatic drainage largely mediates the beneficial effects of PBM, as the ablation of meningeal lymphatic vessels abolishes PBM's effect on cognitive improvement. Additionally, mice treated with PBM exhibited enhancements in mitochondrial metabolism and cellular junctions of meningeal lymphatic endothelial cells, potentially underlying the positive effects of PBM on glymphatic drainage [125]. Taken together, these findings may point to new mechanistic pathways underlying the beneficial effects of transcranial PBM for AD.

Biological mechanisms underlying the benefits of remote PBM for AD

Abdomen-targeted PBM

Over the past few decades, the close communication between the gut microbiome and CNS functions has been increasingly recognized, leading to a concept known as the gut-brain axis [126]. Recent evidence suggests that the gut microbiome may be an important player in the progression of AD [127]. Significantly different gut microbiome compositions have been observed between AD patients and healthy individuals [128, 129]. More importantly, in transgenic rodent models of AD, the transplantation of fecal microbiota from healthy wild-type mice resulted in a marked reduction in amyloid burden and less tau pathology. Conversely, transplantation of microbiota from AD mice induced cognitive impairment and impaired neurogenesis in wild-type mice [130, 131]. Although the precise mechanisms through which the gut

microbiome influences brain function remain elusive, the gut microbiome is increasingly regarded as an attractive target for the prevention and management of AD.

It is also intriguing to note that abdominal PBM irradiation may lead to a change in the composition of the gut microbiome. A 2-week daily abdominal irradiation with PBM (660 nm and 808 nm, continuous wave, total fluence 10 J/cm²) resulted in a significant difference in intestinal flora diversity compared with control animals. Furthermore, in this pilot study, *Allobaculum*, a genus of bacteria that is associated with a healthy microbiome, was significantly increased following PBM irradiation [132]. In a case report, a human participant received PBM treatment (904 nm; pulsed wave, 700 Hz pulse frequency, 861.3 total joules) on his abdomen for 11 weeks, and his microbiome was tested six times before and after treatment. The results showed substantial changes in intestinal flora diversity following PBM treatment, with an increased abundance of beneficial bacteria such as *Akkermansia*, *Faecalibacterium*, and *Roseburia*, and a decreased abundance of potentially pathogenic genera

[133]. While this case study provides valuable insight, it should be noted that this is only one case without any comparison. Also, microbiomes can vary significantly among individuals. Thus, these results have to be viewed with caution. To validate these results, further case-control studies with larger participant cohorts are imperative.

Another recent study reported the potential benefits of employing abdomen-targeted PBM therapy for AD [32] (Fig. 4). In this study, wild-type mice were infused intracerebroventricularly with Aβ and then treated sequentially with 630 nm, 730 nm, and 850 nm abdomen-targeted PBM (continuous wave, 100 J/cm² daily, 5 times a week for 8 weeks). The results demonstrated that PBM at all three wavelengths significantly alleviated Aβ infusion-induced memory impairment, along with reduced amyloidosis and tau phosphorylation in the hippocampus [32]. Moreover, abdomen-targeted PBM led to remarkable alterations in the expression levels of more than 500 proteins involved in hormone synthesis, phagocytosis, and metabolism in the hippocampus [32]. The findings

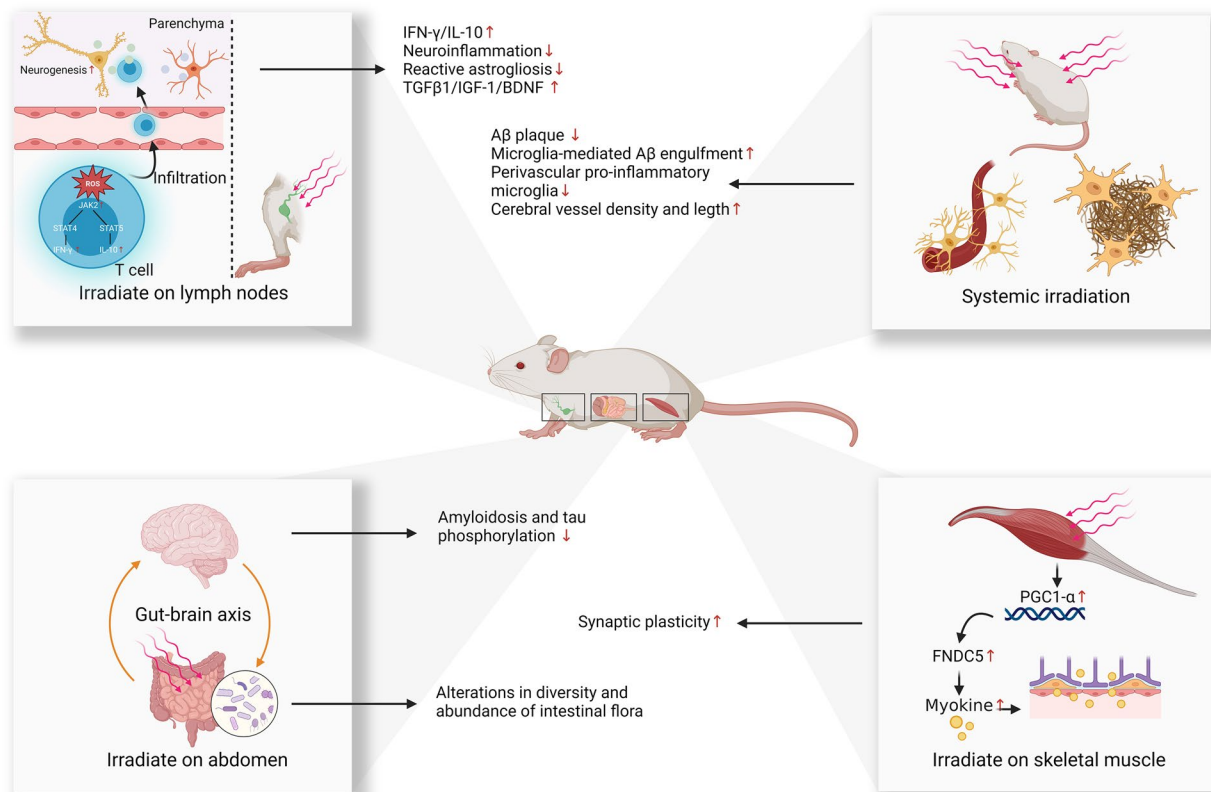


Fig. 4 Proposed mechanisms of action for systemic and remote PBM. Abbreviations: PBM, photobiomodulation; ROS, reactive oxygen species; IFN γ , interferon gamma; IL-10, interleukin 10; TGF β -1, transforming growth factor beta 1; IGF-1, insulin-like growth factor 1; BDNF, brain-derived neurotrophic factor; A β , amyloid beta; PGC1- α , peroxisome proliferator-activated receptor gamma coactivator 1-alpha; FNDC5, fibronectin type III domain-containing protein 5

of a 16S rRNA gene sequencing study further revealed changes in the diversity and abundance of the intestinal flora in AD mice following abdominal irradiation with PBM. The PBM-treated microbiome aligned more closely with the composition of the intestinal microflora in healthy animals [32].

Given that light could penetrate the abdominal region and affect intestinal tissues, abdominal irradiation could be a promising route for PBM delivery, and may potentially benefit AD through the gut-brain axis. Nevertheless, further studies are needed to determine any potential adverse effects and establish a safe dosage.

Lymph node-targeted PBM

Recently, immunotherapy for AD has garnered increasing research interest [134]. CD4+ T cells (commonly known as helper T cells) are one of the key targets in these investigations because they play a pivotal role in the immune response. Once activated in the lymph nodes, CD4 cells can be further recruited into other organs including the brain, where they influence various cellular processes by releasing regulatory cytokines and affecting glial cell activity [135, 136]. Studies have shown that early temporary depletion of regulatory T cells worsens cognitive impairment in experimental mouse models of AD. Conversely, increasing regulatory T cells through peripheral regulation demonstrated the potential to mitigate AD-associated cognitive deficits [137]. This highlights the potential of targeting peripheral immune cell regulation to treat CNS diseases.

A recent study explored the therapeutic potential of PBM targeted to axillary lymph nodes for AD [33] (Fig. 4). When PBM (635 nm, continuous wave, 2 J/cm² at lymph node daily) was applied to the axillary lymph nodes for one month, increased adult hippocampal neurogenesis and fewer cognitive deficits were observed in both APP/PS1 and 3xTg-AD mice. Mechanistically, lymph node-targeted PBM induced reactive oxygen species (ROS) in T cells, thus activating the JAK2/STAT4/STAT5 signaling pathway. This led to increased levels of IFN- γ /IL-10 in non-parenchymal CD4+ T cells [33]. The infiltration of these non-parenchymal CD4+ T cells into the brain subsequently increased the expression of immune mediators IFN- γ /IL-10 in brain tissue, alleviating neuroinflammation and reactive astrogliosis. Additionally, PBM increased the expression levels of TGF β 1/IGF-1/BDNF in the brain [33]. These changes may create an improved microenvironment and foster adult hippocampal neurogenesis. Moreover, culturing neural stem cells derived from AD mice with PBM-treated T lymphocyte-conditioned medium enhanced cell differentiation [33]. These findings suggest a new route for the application of PBM, which could be useful for therapeutic purposes.

Skeletal muscle-targeted PBM

Irisin is a recently discovered myokine, which has garnered considerable attention for its neuroprotective properties [138–140]. Myokines are polypeptides that are produced, expressed, and released by muscle fibers, and exert autocrine, paracrine, or endocrine effects elsewhere in the body. Physical exercise induces an increase in the transcriptional coactivator PGC-1 α in skeletal muscle, leading to elevated expression of fibronectin type III domain-containing protein 5 (FNDC5), which is the membrane-bound precursor of irisin [138]. This precursor is subsequently cleaved into irisin. Circulating irisin can penetrate the blood–brain barrier, where it exerts neuroprotective effects. Irisin is believed to play a pivotal role in the protective mechanisms of physical exercise against AD [141, 142]. Recombinant irisin, administered either intracerebroventricularly or peripherally, was demonstrated to mitigate synaptic deficits and memory impairment in both transgenic AD mice and mice infused with A β [141, 142]. Similar results have been reported with the intracerebroventricular injection of an FNDC5 encoding adenoviral vector [141].

Importantly, PBM can also activate PGC-1 α or increase irisin production when used to irradiate skeletal muscle [143, 144]. Following PBM treatment (0.6 J and 5 J), upregulation of PGC-1 α expression was observed in dystrophic primary muscle cells, with no associated cytotoxicity [144]. Gastrocnemius muscle-targeted PBM (808 nm, continuous wave) applied daily for 2 months resulted in a significant increase in muscle irisin levels, comparable to the effects of 2 months of swimming training [143]. While the effects of skeletal muscle-targeted PBM are under investigation, these preliminary studies suggest the hypothesis that skeletal muscle-targeted PBM may benefit AD by activating PGC1- α /FNDC5 and subsequently producing myokines like irisin. The proposed mechanism is illustrated in Fig. 4.

Systemic PBM therapy for AD

Currently, only a few studies have explored the therapeutic efficacy of systemic PBM for AD. Using a whole-body PBM device fitted with an LED array, one research group investigated the effect of a 60-day PBM treatment (1070 \pm 50 nm, pulsed wave, 10 and 40 Hz, 4.5 J/cm² daily) for AD (Fig. 4) [25]. The results showed that when applied to the entire body of APP/PS1 mice, there was a notable reduction in A β burden in the hippocampus and the cortex [25]. Subsequent experiments revealed that PBM modulated the activation of microglial cells to increase their capacity for the engulfment of A β plaques. Additionally, there was a decrease in perivascular pro-inflammatory microglia and an improvement in vessel density post-PBM treatment [25]. Further analysis using

Pearson correlation coefficients showed a strongly negative correlation between A β burden and vessel density and length. The increased vessel length was also associated with better performance in memory-associated behavioral tests. Notably, a more significant therapeutic benefit was observed with 10 Hz pulsed light compared to continuous wave light, although the underlying mechanism remains unknown.

In summary, this preliminary investigation provided initial evidence supporting the potential of systemic PBM therapy for AD. However, considering that exposing multiple tissues to light may induce a variety of biological effects, further studies are warranted to elucidate the potential mechanism of any crosstalk.

Challenges and solutions

Light penetration and its measurement

In both laboratory studies and clinical practice, transcranial PBM remains the most widely used paradigm. Despite the direct application of light to the head, only a small fraction of the irradiated light reaches the brain tissue due to losses caused by its passage through multiple layers, including the dura, meninges, periosteum, scalp, and skull bone [12]. The inherent differences in the physiological structures of human and laboratory animal skulls make it challenging to extrapolate results from experimental animals to clinical measurements in humans. This fact limits the clinical application of PBM, as there is currently no consensus on the exact transmittance of PBM light through the human brain or the recommended PBM dose received at different brain regions.

The measurement of transcranial PBM in experimental animals typically involves isolating the animal head, cross-sectioning it to expose specific layers such as the cortex and hippocampus, and administering PBM onto the isolated head through the skin and skull. The power value at different depths is then quantified using an optical power meter [51, 145]. However, comparing the skulls of humans to animals reveals a significant attenuation of light energy penetration [146]. The measurement of light emission is also a critical aspect to consider, as it could significantly influence light penetration and absorption [147]. However, the absence of standardized measures of light emission across studies introduces significant variability, stemming from differences in devices and methodologies employed. This variability makes it difficult to directly compare and evaluate the findings across different studies. Consequently, further research is necessary to comprehensively evaluate the biological effects and therapeutic efficacy of PBM using standardized equipment.

A pilot study utilized a chick embryo model situated beneath a human scalp and skull to explore the biological

impact of various laser and LED stimulation systems. The findings revealed that a 10-min session of yellow laser stimulation (at 589 nm) directed through a human skull led to a notable increase in blood volume in the chick embryo model [148]. This finding implies the potential for light penetration through the human skull to induce biological responses [148]. Using an intact human skull, another study investigated the transmission capabilities of various lasers [149]. Remarkably, alongside red (658 nm) and infrared (810 nm) lasers, yellow lasers (589 nm, 50 mW) also exhibited the ability to penetrate the human skull [149]. Moreover, in a formalin-preserved cadaveric model, using an 830 nm LED light source was reported to penetrate soft tissue, bone, and brain parenchyma, but the transmission was only 0.9% [150]. Another pivotal study investigated transcranial light penetration in intact human cadaver heads. The findings suggested that 808 nm wavelength light applied transcranially could penetrate the scalp, skull, and meninges, reaching a depth in the brain of approximately 40–50 mm [151]. While NIR light of other wavelengths can also penetrate the human skull to reach brain tissues, their penetration depths remain relatively low, posing challenges for reaching deeper brain regions [152, 153]. Notably, the penetration of NIR light appears to differ between living and postmortem tissue, emphasizing the limitations inherent in the determination of light penetration obtained using human cadaveric experiments [153].

While the extent to which transcranial PBM can penetrate the human skull may be restricted, several human studies have verified its direct impact on brain activity. For instance, research has shown that transcranial PBM can elicit responses in various brain regions, such as the putamen, primary somatosensory cortex, and parietal association cortex [154]. Moreover, transcranial PBM has been demonstrated to enhance the power of alpha, beta, and gamma brain waves as measured by electroencephalography [155]. The beneficial effects of transcranial PBM using different wavelengths have also been widely reported in patients with various neurological disorders including stroke, traumatic brain injury, AD, and other types of dementia [156–158]. Nevertheless, the failure to measure the light penetration through the skull to specific brain tissue regions hampers accurate dose evaluation in PBM and may hinder its future clinical application. A feasible solution may involve evaluating the penetration of light and measuring the power output with different PBM parameters in fresh, unfixed human cadaver tissue. This approach could establish a reliable foundation for determining the appropriate dosage for PBM therapy. Another option is to develop human head-mimicking models that closely resemble the anatomical and physiological characteristics of the human head, and

integrate implantable optical power sensors for more precise evaluation. Similar challenges need to be overcome in remote PBM therapy. However, since this treatment paradigm is still in its infancy, research on remote PBM should prioritize evaluating its efficacy and understanding its biological mechanisms in experimental animal models.

Intriguingly, recent studies have suggested a novel approach to stimulate deeper brain regions by combining NIR laser with photosensitive nanoparticles [159]. When exposed to optical stimulation from an NIR laser, designed nanodrugs can be released from the photosensitive nanomaterials to targeted brain regions, allowing for more precise regulation of neural activity and stimulation of deeper brain regions [159]. Several studies have demonstrated the efficacy of this therapy combination for AD [160, 161]. This topic has been elegantly reviewed elsewhere [159, 162, 163] and is beyond the scope of this review. Nevertheless, despite the promising initial findings, the safety of this combination therapy requires further investigation.

Biphasic dose–response and determination of the clinical dose

The biphasic dose–response phenomenon describes a non-linear relationship between the applied dose and the resulting biological effects. This is where any treatment induces a beneficial response at a low dose but elicits an inhibitory response at a much higher dose. Notably, these effects (also known as hormesis) have been observed in PBM therapy [164, 165]. In cultured cortical neurons, exposure to 810 nm PBM at 25 mW/cm² resulted in different outcomes at different fluences [166]. At a fluence of 3 J/cm², a maximal increase in ATP production and mitochondrial membrane potential was observed. Conversely, a fluence of 30 J/cm² produced inhibitory effects, causing damage to mitochondria, while lower fluences (0.03 and 0.3 J/cm²) did not induce any discernible biological effects [166]. An experimental study in rats also demonstrated the biphasic dose–response effect of transcranial PBM on CCO activity [167]. CCO activity increased by 14% at a lower dose of 10.9 J/cm², 10% at the higher dose of 21.6 J/cm², and only 3% at the highest dose of 32.9 J/cm² [167]. Consequently, further research is required to assess the effective dose of transcranial PBM before widespread clinical application.

Based on current knowledge obtained from experimental animal studies, postmortem studies, and Monte Carlo simulation, the proposed effective clinical dose for transcranial PBM at the cortical level is 5–10 J/cm² [15]. Notably, several non-human primate models have been established in recent years [168, 169]. Given the resemblance in neuroanatomical structure and higher-order

cognitive functions between non-human primates and humans, it is conceivable that the use of these experimental animal models will contribute significantly to evaluating the effective dose and therapeutic value of transcranial PBM for AD.

Light delivery approach

While the effectiveness of various PBM treatment paradigms for AD-associated pathologies has been explored, little is known about potential differences when light is irradiated onto different tissues. In this sense, further research is required to compare and evaluate the therapeutic efficacy of different PBM paradigms, which may offer valuable insights into the optimal approach for light delivery or alternative treatment options.

Moreover, considering the varied biological effects induced by PBM when applied to different tissues, the combination of multiple different light delivery approaches may potentially yield better results compared to a single light delivery paradigm. A modified PBM technique, involving irradiation onto both the head (850 nm, and 650 nm, pulsed wave, 10 Hz, 8.4 J/cm² at the skin level daily for 7 days) and the abdomen (850 nm and 650 nm, pulsed wave, 10 Hz, 8.4 J/cm² at the skin level daily for 7 days), resulted in reductions in A β , tau, markers of oxidative stress, apoptosis, and inflammation in mice intracerebroventricularly infused with A β , as reported by a research group from France [31]. In another case report, the use of three different wearable LED devices, including a transcranial light helmet (635 nm, continuous wave), a body pad (810 nm, continuous wave), and an intranasal LED device (810 nm, pulsed wave, 10 Hz), used at the same time improved cognitive function in a patient with a history of AD [170]. A case series report demonstrated that the combination of transcranial and intranasal PBM (810 nm, pulsed wave, 10 Hz, 375 or 639 J per week) for 12 weeks significantly improved cognition in five patients with mild to moderately severe cognitive impairment [20]. However, the improved cognitive function conferred by PBM was significantly diminished during the follow-up period (week 16), indicating that continuous application may be necessary to maintain clinical improvements [20]. However, it's crucial to consider the limitations of these case reports, including small sample sizes and lack of control groups, which may limit the generalizability and robustness of the observed outcomes. Further well-designed trials with larger cohorts and rigorous controls are required. In this aspect, a randomized, double-blind, and sham-controlled trial provided robust evidence for the therapeutic value of PBM in cognitive improvement [18]. In this study, 53 mild-to-moderate AD patients were randomly assigned to receive either head-abdomen PBM treatment (40

treatment sessions lasting 25 min each over 8 weeks) or were allocated to a sham treatment group [18]. Following the intervention, patients who received PBM therapy reported improved cognitive performances, measured by neuropsychological tests during the 4-week follow-up assessment, with minimal adverse effects recorded [18]. Furthermore, while safety aspects require further evaluation, another report highlighted the therapeutic potential of intravascular PBM for AD [171]. Under local anesthesia, the common femoral artery of patients was catheterized, and a thin, flexible fiber-optic cable was advanced to the distal sections of the anterior and middle cerebral arteries, where light was irradiated (632 nm, 25 mW, 20–40 min per session). After 6–12 months of daily treatment, improved cerebral microcirculation and metabolism, as well as less cognitive impairment, were reported [171]. These promising findings suggest that the combined application of different PBM paradigms may result in synergistic effects, which remain to be determined in future research. Further investigation into the therapeutic potential of alternative light delivery approaches is therefore warranted.

Clinical translation and application of PBM

In the past decade, considerable advances have been achieved in the use of PBM therapy for AD. Still, several challenges remain to be resolved before the widespread clinical application of this therapy. Research conducted in experimental animal models has significantly advanced our comprehension of the biological mechanisms underlying the beneficial effects of PBM for AD, particularly transcranial PBM therapy. While the beneficial effects of PBM are widely recognized, the precise molecular mechanisms driving these effects are still not fully understood. Historically, CCO has been implicated as the primary target for this therapy, as discussed in the previous sections. However, this foundational hypothesis lacks direct empirical support. Moreover, given the reported various biological effects conferred by PBM, how photoactivated CCO may potentially interact with these cellular processes remains to be determined. A better understanding of the fundamental mechanism of PBM will provide insight into the rational design and application of this therapy.

Despite the widely reported beneficial effects of PBM on animal models of AD, a recent study [172] found no significant impact of PBM. In this randomized, blinded study, 5xFAD mice received transcranial PBM treatment (810 nm, pulsed wave at 100 Hz, three times a week) from 1 month old to 6 months old. The results revealed no discernible differences in memory performance, amyloid load, neuronal loss, or microglial response between the 5xFAD mice treated with PBM and the control group

[172]. This outcome may be attributed to variations in light parameters/treatment dosage and the devices utilized. It is worth noting that many animal studies neglect to report crucial light parameters such as light power output on target tissues and waveform, potentially leading to discrepancies even when employing the same light wavelength. Therefore, the findings of these preclinical studies should be approached with caution, and more standardized studies are required in the future.

Further evaluation of the penetration of different light parameters through the skull to reach brain tissue and the effects of power output on specific brain regions is warranted. Potential approaches include measuring these parameters in fresh, unfixed human cadavers or human head-mimicking models, as discussed earlier, which could provide better control over the effective light dose. Despite the proposal of a variety of light delivery approaches, their efficacy, mechanisms of action, and safety must be thoroughly investigated in experimental animals before any clinical application, making this a priority. The therapeutic potential of the combination of various light delivery approaches also warrants further validation in animal models.

The therapeutic potential of transcranial PBM for AD has been documented in various clinical trials and case reports, where it has demonstrated only minimal side effects. However, given the observed biphasic dose response in cultured neural cells and animal models, coupled with the complexity of AD pathogenesis, it is crucial to conduct further investigation to determine the effective dose of transcranial PBM in large animal models that are both physiologically and anatomically nearer to humans. In this context, recently developed non-human primate models of AD may serve as a tool for addressing these concerns and may provide valuable insight into clinical applications.

Furthermore, it is crucial to acknowledge that the majority of preclinical studies have primarily involved rodent models. The structural and anatomical differences between these experimental animals and human beings pose a challenge in translating these findings from the laboratory into clinical practice. The discrepancy in brain size between small experimental animals also presents a significant hurdle for translating this therapy. While light can penetrate the entire brain of animals, reaching deeper brain regions like the dorsal hippocampus and amygdala [145], achieving similar coverage in humans is challenging, with most light only reaching the cortical level. Consequently, the doses administered and resulting biological effects may vary significantly between rodents and humans. The full extent of PBM's effects on a human scale remains to be determined. In this regard, some completed

randomized controlled trials may offer valuable insights into the therapeutic efficacy of this therapy in humans. In a small randomized controlled trial, thirty-two dementia patients were randomly assigned to either receive 8 weeks of transcranial PBM therapy or a sham intervention. The evaluation revealed that those who received transcranial PBM showed improved cognitive symptoms compared to those who underwent the sham procedure [173]. Similarly, another randomized clinical trial investigated the impact of combined PBM and aerobic exercise on cognitive function in elderly AD patients [174]. Sixty elderly AD patients were randomly divided into two groups: one receiving PBM (intravascular and intranasal PBM, 30 min per session, twice a day, three days a week) alongside moderate-intensity aerobic exercise, and the other receiving a placebo intervention in addition to aerobic exercise over 12 weeks. Results indicated that patients who received PBM alongside moderate-intensity aerobic exercise exhibited significant improvements in cognition, life quality, and balance function compared to the control group receiving placebo therapy alongside aerobic exercise [174]. Moreover, the most robust evidence stems from a randomized and double-blind trial, demonstrating that a two-month head-abdomen PBM treatment yielded slight cognitive improvement, as discussed in previous sections [18]. Although the treatment duration was relatively short compared to current clinical trials on AD therapeutic intervention, typically lasting 18 months [175, 176], this preliminary trial is encouraging as it

suggests that a relatively short treatment period for this therapy may be sufficient to produce favorable outcomes to some extent. Furthermore, no obvious adverse events were reported in these studies, suggesting this therapy may have a better safety and tolerability profile compared to conventional pharmacological methods. Nevertheless, to confirm the efficacy and determine the optimal dosage of this therapy in AD, it is crucial to conduct further large-scale, methodologically rigorous, randomized controlled trials involving a more extensive patient population. Moreover, extending the treatment duration is essential for a comprehensive evaluation of its overall effects. Several registered clinical trials are currently underway (JRCTs032230339, NCT05926011, NCT04784416, NCT03484143), involving multi-site participation, larger sample sizes, and longer treatment durations, which are expected to provide additional insights into the clinical application of PBM.

Notably, it may be unable to make an effective comparison of therapeutic efficacy in different studies due to the unstandardized instruments and measurement methods. Indeed, based on different parameters such as wavelengths, wave mode (continuous wave and pulsed wave), irradiance, fluence, and treatment protocols, the effects of PBM treatments can vary, which may yield different outcomes. Thus, PBM may not be considered a standardized treatment with guaranteed safety and efficacy across the board. Each specific combination of parameters and protocols needs to be evaluated individually as a unique medical device.

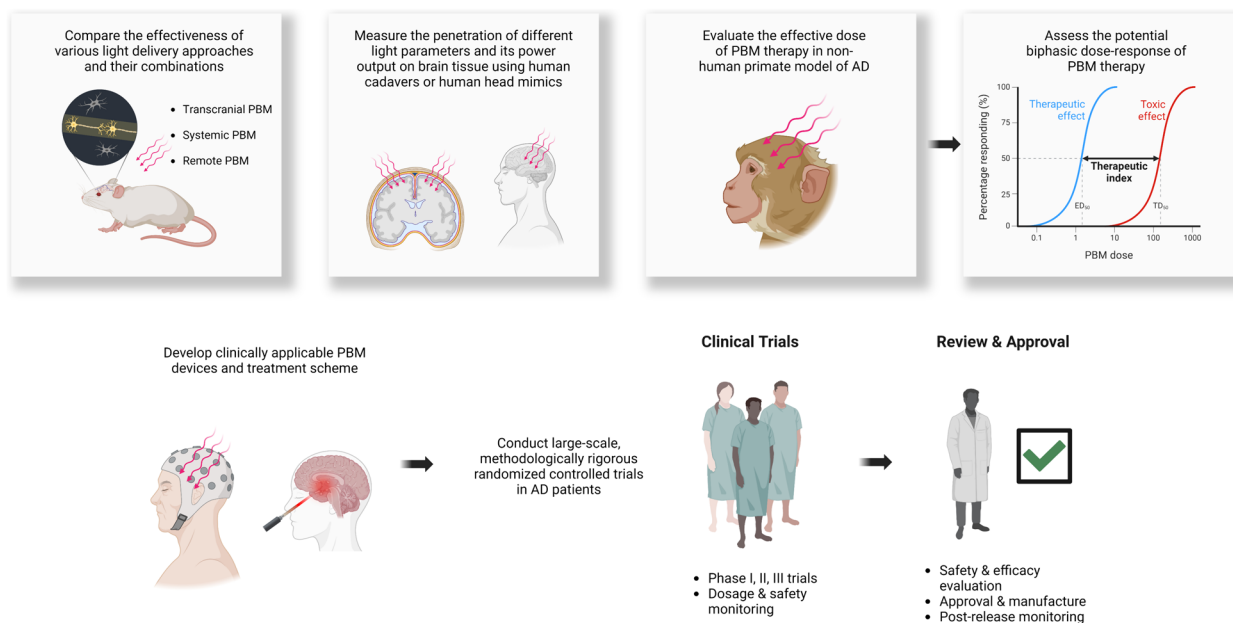


Fig. 5 Summary of directions for future research and the clinical translation of PBM therapy. Abbreviations: PBM, photobiomodulation; AD, Alzheimer's disease; CSF, cerebrospinal fluid

Given the lengthy pre-clinical asymptomatic phase of AD and the limited effectiveness of existing therapies for AD patients, preventive intervention has emerged as a promising approach for AD management [177, 178]. Technological advancements have led to the identification of several early biomarkers of AD, offering the potential for early disease detection and extending the window for timely intervention [179–181]. Advances in neuroimaging techniques will also enable precise neurological and structural evaluation, potentially allowing for the identification of early pathological alterations associated with AD [182]. To date, clinical trials in this field have predominantly focused on patients with confirmed AD. Yet, with advancements in identifying early AD pathological changes and refining safe treatment protocols from subsequent trials, it would be attractive to explore if early PBM treatment could slow down the progression of AD, which may be more clinically meaningful and may offer better control over the overall disease burden (Fig. 5). Future studies into this field could potentially pave the way for a novel direction in the management of AD.

Conclusions

The multifactorial nature of AD and its complex pathogenesis underscore the need for multimodal and individualized treatment interventions. As a non-invasive and non-pharmacological intervention, PBM therapy, especially transcranial PBM, has shown the potential to prevent and/or alleviate AD-associated pathology and cognitive decline. Current knowledge suggests that PBM can activate various signaling pathways within the brain, exerting a variety of beneficial biological effects. Accumulated evidence from both experimental animal studies and clinical trials supports its potential in AD management, with only minimal side effects. Thus, it is time to begin to translate this promising therapy from the laboratory bench to the bedside. Importantly, while existing evidence suggests the potential of PBM as a therapeutic intervention for AD, further clinical trials are imperative to thoroughly assess its efficacy and establish treatment protocols. Such endeavors hold promise of introducing novel opportunities for the safe and effective management of AD.

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ZH reviewed the literature and drafted the manuscript. ZH and QZ conceived and designed the review, QZ and MRH revised the manuscript. All authors read and approved the final manuscript.

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